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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,899	09/28/2001	Markku Koulu	2630-111	5535

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,899	KOULU ET AL.	
	Examiner	Art Unit	
	Amy H Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 4,2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,14 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The amendment filed 8/30/2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO:9 is not in the original disclosure or sequence listing. Applicant points to page 7, line 12 – page 8, line 8 of the specification to support the amendment filed 8/30/2004, which adds SEQ ID NO:9. However, there is no support at page 7, line 12 – page 8, line 8 of the specification because SEQ ID NO:9 replaced a different sequence. Support could not be found elsewhere in the originally filed application, including the sequence listing.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of applicant's amendments (8/30/2004), the previous written description rejection to claims 8, 14 and 15 are withdrawn due to cancellation of claim 15 and the amendments to claims 8 and 14.

Claims 8, 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Upon applicant's amendments to the claims, filed 8/30/2004, the claims are drawn to SEQ ID NO:9. The original sequence listing and the original specification do not have support for SEQ ID NO:9, resulting in new matter. Applicant points to page 7, line 12 – page 8, line 8 of the specification to support the amendment filed 8/30/2004, which adds SEQ ID NO:9. However, there is no support at page 7, line 12 – page 8, line 8 of the specification because SEQ ID NO:9 replaced a different sequence.

Claims 8, 14 and 16 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record in the official office action of 1/15/2004 (i.e. pp 6-15) and reiterated in the advisory action 9/22/2004, and further in consideration of the amendments filed 8/30/2004. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims are drawn to methods of preventing retinopathy in diabetic persons with an increased risk of developing diabetic retinopathy, due to the presence of a mutation of amino acid 7 of preproNPY from leucine to proline, by the administration of agents that counteract the influence of the mutant NPY gene.

At the time the invention was made, the skilled artisan would not reasonably expect success in practicing the method claimed with SEQ ID NO:9 to reduce the risk of developing diabetic retinopathy in any diabetic person, due to the lack of data presented as well as the lack of therapeutic applications for reducing risk of diabetic retinopathy in the art. The claims are not enabled for any treatment, *in vivo*, or *ex vivo* by any agent that counteracts the mutant gene.

Further, the antisense oligonucleotide of claims 8 and 14 do not require full complementarity with SEQ ID NO:9. The claims read on partial complements to SEQ ID NO:9, which would be even less likely to inhibit the NPY gene. Additionally, claims 8, 14 and 16 are not only drawn to the treatment of a diabetic person, which has not been experimentally demonstrated in the specification or the art, but are also drawn to the prevention of developing diabetic retinopathy, which has not been demonstrated. Applicant has not presented data that would suggest that it can be determined if the individual would have developed diabetic retinopathy to demonstrate that it would be prevented by the administration of a particular oligonucleotide. Applicant has only shown secondary structure predictions, which does not actually predict the activity of a specific antisense oligonucleotide or the degree of activity needed for treatment.

The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art

due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Branch (TIBS 1998, vol. 23, p. 45-50), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects, resulting in the need for each antisense sequence to be tested individually.

Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNS can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in humans, with a resultant treatment and inhibition of gene expression, as claimed. Although applicant discloses a specific target

sequence (SEQ ID NO:9), secondary structure of the sequence does not predict which antisense sequences would be appropriate or successful for treatment in a human. Applicant argues that the sequence has been disclosed to contain bulbs, which are recognized by a skilled artisan to enhance binding of antisense oligonucleotides. This does not overcome the enablement requirement of treatment and prevention utilizing this particular sequence. Disclosing the target sequence is not sufficient support to demonstrate which sequences would be appropriate antisense oligonucleotides to inhibit expression. Empirical evidence is needed to support a specific sequence. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of expression of a target gene. One of skill in the art would not know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in humans. The field of antisense therapeutics does not provide that

guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

In order to practice the claimed invention *in vivo* in humans, a number of variables would have to be optimized, including 1). determining what sequences would constitute antisense sequences capable of binding to SEQ ID NO:9 and what antisense sequences would actually bind to SEQ ID NO:9 and form a strong enough complex that they would be effective at modulating apoptosis, 2). the form of the antisense or decoy oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 3). the mode of delivery of the antisense or decoy oligonucleotide to an organism that would allow it to reach the targeted cell, 4). the amount of antisense or decoy oligonucleotide that would need to be delivered in order to bind a sufficient amount of SEQ ID NO:9 to modulate apoptosis once it reached the proper cell and 5). ensuring the antisense or decoy oligonucleotide remains viable in a cell for a period of time that allows modulation of apoptosis to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense or decoy oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 8, 14 and 15 are not enabled.

Respons to Arguments

Applicant's arguments filed 11/04/2004 have been fully considered but they are not persuasive. Applicant argues that Lebedeva et al. not only describe difficulties associated with antisense therapy, but also describe techniques that have been used to overcome such difficulties. Applicant argues that these techniques demonstrate that solutions to the difficulties can be achieved without undue experimentation. This argument is not considered persuasive because the antisense field teaches that undue experimentation is required to treat using a specific antisense oligonucleotide, as discussed in the previous rejections (official office action of 1/15/04, page 10; official office action of 6/30/04, pages 6-9). While Lebedeva provides for a promising future, it does not enable applicant's gene therapy invention, because antisense gene therapy is unpredictable and specific for each disease, gene, vector and route of administration as demonstrated in the references applied in the rejections of record.

Applicant argues that the examiner based their conclusion on one reference. The examiner cited various references to support the enablement rejection in the official office action mailed on 1/15/04, followed by Lebedeva et al. in the official office action mailed on 6/30/2004. These references support that the state of the field of antisense is such that inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is unpredictable for several reasons, including the problems of delivery, specificity and duration. Applicant argues that Robinson et al. and Formivirsen support therapeutic effect in ocular indications. Although Robinson et al. and Formivirsen have had positive results, this does not enable the entire field of antisense therapy for ocular indications. Robinson et al. and

Formivirsen are specific examples of local delivery with specific oligonucleotides, neither of which is being instantly claimed.

Applicant argues that U.S. published patent application 2004/0006004 A1 demonstrates that an antisense oligonucleotide directed to the NPY Y2 receptor mRNA is effective *in vivo* for treating retinopathy in rats. This is a post-filing patent application that teaches a specific target and a specific antisense oligonucleotide, which does not enable the invention being instantly claimed at the time of filing and offers guidance missing from the instant specification. In addition to the application teaching specific elements that are not instantly claimed, this is a patent application that has not been examined.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:30 am – 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
Examiner
Art Unit 1635

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER